

Genetic risk score predicting accelerated progression from mild cognitive impairment to Alzheimer's disease

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Summary

Aside from APOE, the genetic factors that influence in the progression from mild cognitive impairment (MCI) to Alzheimer's disease (AD) remain largely unknown. We assessed whether a genetic risk score (GRS), based on 8 non-APOE genetic variants previously associated with AD risk in genome-wide association studies, is associated with either risk of conversion or with rapid progression from MCI to AD. Among 288 subjects with MCI, follow-up (mean 26.3 months) identified 118 MCI-converters to AD and 170 MCI-nonconverters. We genotyped ABCA7 rs3764650, BIN1 rs744373, CD2AP rs9296559, CLU rs1113600, CR1 rs1408077, MS4A4E rs670139, MS4A6A rs610932, and PICALM rs3851179. For each subject we calculated a cumulative GRS, defined as the number of risk alleles (range 0-16) with each allele weighted by the AD risk odds ratio. GRS was not associated with risk of conversion from MCI to AD. However, MCI-converters to AD harboring 6 or more risk alleles (second and third GRS tertiles) progressed 2-fold more rapidly to AD when compared with those with less than 6 risk alleles (first GRS tertile). Our GRS is a first step toward development of prediction models for conversion from MCI to AD that incorporate aggregate genetic factors.

Keywords: Mild Cognitive Impairment, Alzheimer's disease, Conversion, Genetics, Risk, Genetic Risk Score

Introduction

There has been a lot of interest in the detection of predictors of conversion from mild cognitive impairment (MCI) to Alzheimer's disease (AD) using neuroimaging methods, CSF biomarkers and cognitive tests (Jack et al., 2010; Landau et al., 2010; Davatzikos et al., 2011). Despite the many genetic studies of AD, there has been little research directed toward determining the influence of genetic variation on progression from MCI to AD (Reitz and Mayeux 2010). While the $\epsilon 4$ allele of APOE is the major genetic risk factor for AD, recent genome-wide association studies (GWASs) have identified several susceptibility loci for AD (Harold et al., 2009; Lambert et al., 2009; Seshadri et al., 2010; Hollingworth et al., 2011; Naj et al., 2011), but most of these risk alleles have shown only a modest effect (odds ratios between 0.88 and 1.23). Previous studies have shown that combining multiple loci with modest effects into a global genetic risk score (GRS) might improve identification of persons who are at risk for common complex diseases, such as coronary heart disease (Ripatti et al., 2010), type 2 diabetes (Cornelis et al., 2009), rheumatoid arthritis (Karlson et al., 2010), or multiple sclerosis (De Jager et al., 2009). To our knowledge, no study has examined the joint effects of previously reported AD-predisposing loci derived from GWASs on the risk of conversion from MCI to AD.

We investigated the relationship between 8 non-APOE AD risk alleles (ABCA7 rs3764650, BIN1 rs744373, CD2AP rs9296559, CLU rs1113600, CR1 rs1408077, MS4A4E rs670139, MS4A6A rs610932, and PICALM rs3851179), considered individually and as cumulative GRS, with two goals: first to characterize the conversion risk from MCI to AD, and then to investigate the velocity of progression in MCI-converters to AD.

Material and methods

Subjects

We examined 297 consecutive patients who attended the Departments of Neurology of University Hospital “Marqués de Valdecilla” (Santander, Spain), Hospital de la Santa Creu i Sant Pau (Barcelona, Spain), and Clínica Universidad de Navarra (Pamplona, Spain) and that fulfilled the Petersen criteria for amnesic MCI (Petersen et al., 2001). The time of onset of MCI was ascertained from informants’ estimates. All patients underwent a complete clinical and neuropsychological evaluation at baseline and at 6-month intervals. General cognitive function was assessed using MMSE, data on activities of daily living were collected using the Interview for Deterioration in Daily living activities in Dementia (IDDD), and symptoms of depression were measured using the Hamilton Rating Scale for Depression.

Neuropsychological battery included test for the assessment of memory (California Verbal Learning Test-CVLT), language and semantic memory (15-items short-form of the Boston Naming Test, category fluency), praxis and visuospatial skills (Rey complex figure copy and WAIS block design subtest), attention and executive function (Symbol Digit Modalities Test, Trail Making part A and B, Stroop interference Test, Frontal Assessment Battery, category and letter fluency). A cognitive domain was judged as impaired when subjects scored 1.5 SD below values for age and education matched controls in at least one test. The development of dementia was established by consensus between the group members (at least 2 neurologists and 1 neuropsychologist) when a functional and/or neuropsychological decline was observed, and patient fulfilled DSM-IV criteria for dementia and NINCDS-ADRDA criteria for AD.

During the follow-up period, 118 MCI patients were diagnosed as MCI-converters to AD (51% women; mean age 75.2 years, SD 5.6, range 60-89 years; mean follow-up 26.3 months, SD 13.2, range 5-82 months); nine additional MCI patients converted to non-AD dementias (dementia with Lewy bodies in five, frontotemporal dementia in two, and vascular dementia in two others). 170 MCI were classified as MCI-nonconverters to AD (47% women; mean

age 73.2 years, SD 6.5, range 57-86 years; mean follow-up 26.3 months, SD 12.7, range 12-72 months).

Genotyping.

Blood samples were taken after written informed consent had been obtained from the subjects or their representatives. The study was approved by the ethical committees of the University Hospital “Marqués de Valdecilla”, Hospital de la Santa Creu i Sant Pau, and Clínica Universidad de Navarra. Genotyping of ABCA7 rs3764650, BIN1 rs744373, CD2AP rs9296559, CLU rs1113600, CR1 rs1408077, MS4A4E rs670139, MS4A6A rs610932, and PICALM rs3851179 was performed using a Taq-Man single-nucleotide-polymorphism assay (Applied Biosystems, Warrington, Cheshire, UK) and an ABI PRISM 7000 or 7900HT sequence detection systems (Applied Biosystems). References for each of the selected genes and single nucleotide polymorphisms are provided with the AlzGene database (Bertram et al., 2007). We used a dominant model comparing the homozygote for the non-risk allele to the combined heterozygote and homozygote for the risk allele.

Statistical analysis.

In addition to assessing each individual SNP (Model 1), we developed a weighted GRS (Model 2) where the weight is the allelic odds ratio for each allele as described in AlzGene database (Bertram et al., 2007). The weighted GRS was calculated by multiplying the number of risk alleles for each SNP (0, 1, or 2) by the weight for that SNP, and then taking the sum across the 8 SNPs. We divided the continuous GRS into tertiles and compared risk between them. Logistic regression was used to assess whether the conversion risk from MCI to AD was associated with the individual SNPs or the GRS divided into tertiles. Cox regression was used to assess the association with time-to-conversion. To exclude the possibility that differences in both the conversion risk and time-to-conversion were due to the dominant role of APOE ϵ 4 allele, GRS was calculated without the largest effect size of APOE ϵ 4 allele.

Since each of the 8 reported SNPs has previously been associated with AD at significance levels exceeding a stringent GWAS threshold AD ($P < 5 \times 10^{-8}$) (Harold et al., 2009; Lambert et al., 2009; Seshadri et al., 2010; Hollingworth et al., 2011; Naj et al., 2011), we did not perform a Bonferroni adjustment and in this report we regarded an association to be significant if a two-sided p-value was less than 0.05 (for the same risk allele in the same direction as in the original report).

Results

As shown in Model 1, we first examined each individual genetic variant for both conversion risk from MCI to AD (Table 1) and velocity of conversion in MCI-converters to AD (Table 2), with APOE $\epsilon 4$ allele being significantly associated with conversion risk (OR = 4.63, 95% CI = 2.15-9.98, $p < 0.001$) and rapid progression (HR = 1.77, 95% CI = 1.05-2.97, $p = 0.03$). In addition, CLU (rs1113600) was associated with a decreased conversion risk (Table 1, OR = 0.25, 95% CI = 0.07-0.84, $p = 0.025$), whereas CD2AP (rs9296559) conferred a marginally significant association with a more rapid progression to AD (Table 2, HR = 1.69, 95% CI = 0.99-2.85, $p = 0.051$).

In model 2, we next evaluated the joint effects of the 8 non-APOE SNPs as a cumulative GRS, and GRS (adjusted for age, sex and APOE) was not associated with risk of conversion from MCI to AD (Table 1). However, MCI-converters to AD harboring 6 or more risk alleles progressed 2-fold more rapidly to AD compared with those having less than 6 risk alleles (Table 2): both MCI-converters in the second GRS tertile (mean GRS = 6.9, Hazard Ratio = 1.89, 95% CI = 1.01-3.56, $p = 0.047$) and in the third GRS tertile (mean GRS = 9.9, HR = 2.06, 95% CI = 1.07-3.98, $p = 0.031$) showed a faster progression when compared with those in the first GRS tertile (mean GRS = 4.6). Cox survival analysis graph (Fig. 1) showed that MCI-converters in the second and third GRS tertiles progressed more rapidly to AD

(mean time to conversion 26.4 months, SD 10.8) than MCI-converters in the first GRS tertile (mean time to conversion 31.2 months, SD 18.9). We did not explore the correlation between GRS and severity of AD development.

Discussion

MCI patients with the APOE ϵ 4 allele have been described to be more likely to convert to AD as compared to those without the APOE ϵ 4 allele (Elias-Sonnenschein et al., 2011), but these studies of MCI conversion to AD frequently do not account for time-dependent progression (Reitz and Mayeux, 2010). In our series, APOE ϵ 4 allele was significantly associated with both an increased conversion rate from MCI to AD and a shortened time-to-progression; consistent with these results, we recently also observed that APOE ϵ 4 allele reduced time-to-progression in MCI-converters (Samaranch et al., 2010). The extent to which genetic variability other than APOE influences the conversion from MCI to AD is unknown (Cervantes et al., 2011). Microtubule-associated protein tau (MAPT H1/H2) H1/H1 haplotype (Samaranch et al., 2010), vascular endothelial growth factor (VEGF rs699947) AA genotype (Chiappelli et al., 2006), brain-derived neurotrophic factor (BDNF rs6265) Met allele (Forlenza et al., 2010), and butyrylcholinesterase (BuChE rs1803274) Wt allele (Ferris et al., 2009) were associated with a higher risk of AD-conversion in MCI patients. In addition, MAPT H1/H1 (Samaranch et al., 2010), alpha 1-antichymotripsin (SERPINA3 rs4934) AA+AT genotypes (Barabash et al., 2009), and caspase-1 (CASP1 rs580253) CT+TT genotypes (Pozueta et al., 2011) were associated with a shortened time-to-progression in MCI-converters to AD.

It is not clear how to utilize genetic information for prediction of conversion risk from MCI to AD in clinical practice. A critical first step is to understand the role of aggregate genetic risk factors (GRS) rather than the association of individual alleles with this risk.

Toward this end, we selected 8 SNPs that had a strong association with AD in recently published GWASs (Harold et al., 2009; Lambert et al., 2009; Seshadri et al., 2010; Hollingworth et al., 2011; Naj et al., 2011), to derive an aggregate GRS in MCI patients. We found that GRS did not show a good discrimination between MCI-converters and MCI-nonconverters to AD (Table 1). However, while the 8 non-APOE SNPs had little or no predictive power individually, their combined addition in a composite GRS predicted an accelerated progression to AD in MCI-converters (Table 2): MCI-converters in the second and third GRS tertiles had a 2-fold more rapid progression to AD than those in the first GRS tertile, accelerating the progression by an average of 5 months. Notably, the predictive capability of accelerated progression for the APOE $\epsilon 4$ allele alone ($HR = 1.77$) was nearly as good as that of the other 8 non-APOE loci combined in the GRS. The period of clinical follow-up of MCI was relatively short with a mean follow-up time of 26.3 months. An ever more extensive follow-up time of MCI-nonconverters to AD patients in our study might increase the specificity of our GRS as predictor of conversion from MCI to AD, because some of the MCI-nonconverters to AD might still develop AD later on. However, examining the time-dependent evolution of MCI to dementia over an observation period of 6 years, Busse et al. (2006) found that conversion rates to dementia in people with MCI were highest during the first interval of observation, which was 18 months in that study. We did not evaluate any biomarker to predict conversion and reinforce our genetic analysis.

For each patient, the identification of a single polymorphism that is common in the general population but has a small risk effect is not informative. Our study demonstrates the feasibility and potential utility of simultaneously considering the joint effects of 8 common genetic variants aggregated as a GRS, to predict a more rapid progression in MCI-converters to AD. These data need to be confirmed in further studies, and as new susceptibility variants are identified, GRS will need to be periodically updated.

Acknowledgement

C. Sánchez-Quintana was involved in the DNA sample collections from Santander. This study was supported by grants from CIBERNED (CB06/07/0037) and from the Department of Health of the Government of Navarra (refs. 13085 and 3/2008).

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Figure 1. Effect of genetic risk score (GRS) divided into tertiles on survival time (Cox survival analysis graph) to Alzheimer's disease (AD) in patients with mild cognitive impairment (MCI). The y-axis shows the cumulative proportion of MCI-nonconverters to AD for any given follow-up period on the x-axis.

Table 1. Predictive variables of conversion from Mild Cognitive Impairment to Alzheimer's disease

Variable	Odds Ratio	95% CI	<i>p</i> -value
<i>MODEL 1*</i>			
APOE ε4 allele vs non-ε4 allele carriers	4.63	2.15 – 9.98	<0.001
ABCA7 (rs3764650) G allele vs non-G allele carriers	1.80	0.75 – 4.31	0.183
BIN1 (rs744373) G allele vs non-G allele carriers	1.69	0.81 – 3.54	0.157
CD2AP (rs9296559) C allele vs non-C allele carriers	1.50	0.71 – 3.16	0.280
CLU (rs11136000) T allele vs non-T allele carriers	0.25	0.07 – 0.84	0.025
CR1 (rs1408077) T allele vs non-T allele carriers	1.03	0.47 – 2.26	0.934
MS4A4E (rs670139) T allele vs non-T allele carriers	1.15	0.49 – 2.68	0.734
MS4A6A (rs610932) T allele vs non-T allele carriers	1.26	0.43 – 3.70	0.667
PICALM (rs3851179) A allele vs non-A allele carriers	0.49	0.16 – 1.46	0.203
<i>MODEL 2**</i>			
APOE ε4 allele vs non-ε4 allele carriers	4.56	2.23 – 9.38	<0.001
GRS 2 nd tertile vs 1 st tertile**	1.43	0.61 – 3.34	0.407
GRS 3 rd tertile vs 1 st tertile**	1.32	0.57 – 3.06	0.505

*Odds ratio tested with logistic regression model adjusted for age, sex, APOE, ABCA7, BIN1, CD2AP, CLU, CR1, MS4A4E, MS4A6A, and PICALM. ** Odds ratio tested with logistic regression model adjusted for age, sex, APOE, and GRS (see methods for Genetic Risk Score calculation) divided into tertiles

Table 2. Predictive variables of rapid progression in Mild Cognitive Impairment-converters to Alzheimer's disease

Variable	Hazard Ratio	95% CI	<i>p</i> -value
<i>MODEL 1*</i>			
APOE ε4 allele vs non-ε4 allele carriers	1.77	1.05 – 2.97	0.030
ABCA7 (rs3764650) G allele vs non-G allele carriers	1.25	0.68 – 2.28	0.459
BIN1 (rs744373) G allele vs non-G allele carriers	1.31	0.77 – 2.23	0.315
CD2AP (rs9296559) C allele vs non-C allele carriers	1.69	0.99 – 2.85	0.051
CLU (rs11136000) T allele vs non-T allele carriers	0.84	0.39 – 1.80	0.666
CR1 (rs1408077) T allele vs non-T allele carriers	1.15	0.66 – 1.97	0.613
MS4A4E (rs670139) T allele vs non-T allele carriers	0.92	0.49 – 1.72	0.802
MS4A6A (rs610932) T allele vs non-T allele carriers	1.42	0.61 – 3.30	0.416
PICALM (rs3851179) A allele vs non-A allele carriers	0.56	0.25 – 1.24	0.155
<i>MODEL 2**</i>			
APOE ε4 allele vs non-ε4 allele carriers	1.60	0.98 – 2.60	0.057
GRS 2 nd tertile vs 1 st tertile **	1.89	1.01 – 3.56	0.047
GRS 3 rd tertile vs 1 st tertile **	2.06	1.07 – 3.98	0.031

*Hazard ratio tested with Cox regression model adjusted for age, sex, APOE, ABCA7, BIN1, CD2AP, CLU, CR1, MS4A4E, MS4A6A, and PICALM. ** Hazard ratio tested with Cox regression model adjusted for age, sex, APOE, and GRS (see methods for Genetic Risk Score calculation) divided into tertiles